Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

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Daiichi Sankyo Hypertension Franchise Fact Sheet

- An estimated 80 million people, or about 1 in 3 U.S. adults (32.6 percent), have hypertension (high blood pressure).[1] Research shows that lowering high blood pressure reduces the risk of both fatal and non-fatal cardiovascular events, such as strokes and heart attacks. Most people with hypertension will require more than one antihypertensive medication to achieve and maintain blood pressure control.[2]

- Daiichi Sankyo, Inc. (DSI) is committed to the long-term health and wellness of patients, with a hypertension franchise that offers a wide range of hypertension therapies, programs and management tools to help patients work toward their goal blood pressure.

Hypertension Treatment Options

- The DSI portfolio of antihypertensive therapies offers a diverse treatment platform that provides blood pressure reductions for a wide variety of patients with hypertension. The portfolio includes 15 different dose strength combinations across four products, offering both physicians and patients the flexibility in finding a treatment to help them work toward blood pressure goals:

    - **BENICAR®** (olmesartan medoxomil) – The first drug in the DSI hypertension franchise, **BENICAR** is an angiotensin receptor blocker (ARB) that can provide blood pressure reductions to help achieve blood pressure goals.

    - **BENICAR HCT®** (olmesartan medoxomil, hydrochlorothiazide) – The combination of **BENICAR** and the diuretic, hydrochlorothiazide.

    - **AZOR®** (amlodipine, olmesartan medoxomil) – The dual combination of **BENICAR** and amlodipine, a calcium channel blocker (CCB).

    - **TRIBENZOR®** (olmesartan medoxomil, amlodipine, hydrochlorothiazide) – Combines three complementary agents – an ARB, CCB and diuretic – to help patients work toward their blood pressure goals.

- **BENICAR, BENICAR HCT, AZOR** and **TRIBENZOR** have more than 53 million patient-years of use worldwide since 2002 to treat hypertension.

Value-Added Programs to Help Patients Reach Goal

In addition to the prescription portfolio, DSI offers services to help patients work toward their hypertension goals. These include the following patient support programs:

- **Hypertension Care** – A comprehensive blood pressure program designed to help with some of the challenges of hypertensive patients. Components of this program include:

    - A patient reimbursement hotline

- A patient-focused Blood Pressure Support Hotline where patients learn more about high blood pressure and their medications from a registered nurse. The hotline does not provide medical advice and patients are advised to talk to their healthcare provider if they are seeking medical advice.
- A Pre-actived Co-Pay Savings Card to offer potential savings for eligible patients.
- Product samples so that patients can find the right drug and dosage before they pay for an entire prescription.
- Distribution of blood pressure monitors so that patients can help track their blood pressure at home.

- **Right Fit Blood Pressure Program** – A customized patient education program that offers enrolled hypertension patients the option to receive educational articles, healthy recipes, daily medication reminders, refill reminders and practical diet and exercise tips. Eligible patients may utilize the Pre-activated Co-pay Savings Card for potential additional savings.

- **Medication Therapy Management Programs** – DSI, in partnership with both chain and independent pharmacies, provide services for patients such as hypertension education materials right at the pharmacy counter.

About Daiichi Sankyo

- Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets.

- With over 100 years of scientific expertise and a presence in more than 20 countries, Daiichi Sankyo and its 17,000 employees around the world draw upon a rich legacy of innovation and a robust pipeline of promising new medicines to help people. In addition to its strong portfolio of medicines for hypertension, dyslipidemia, bacterial infections, and thrombotic disorders, the Group's research and development is focused on bringing forth novel therapies in cardiovascular-metabolic diseases, pain management, and oncology, including biologics. For more information, please visit: www.daiichisankyo.com.

- Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit www.dsi.com.

Important Safety Information for BENICAR®, BENICAR HCT®, AZOR®, and TRIBENZOR®

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue BENICAR, BENICAR HCT, AZOR, or TRIBENZOR as soon as possible**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS AND PRECAUTIONS: Fetal Toxicity**

CONTRAINDICATIONS

Do not co-administer aliskiren with BENICAR, BENICAR HCT, AZOR, or TRIBENZOR in patients with diabetes.

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BENICAR HCT and TRIBENZOR are contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS AND PRECAUTIONS

Morbidity in Infants: Children <1 year of age must not receive BENICAR for hypertension.

Fetal Toxicity: BENICAR, BENICAR HCT, AZOR, and TRIBENZOR are **Pregnancy Category D**.

Hypotension in Volume- or Salt-Depleted Patients: In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (eg, those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with BENICAR, BENICAR HCT, AZOR, or TRIBENZOR.

Impaired Renal Function: Monitor for worsening renal function in patients with renal impairment while on BENICAR, BENICAR HCT, AZOR, or TRIBENZOR.

In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure), treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Similar results may be anticipated in patients treated with BENICAR, BENICAR HCT, AZOR, and TRIBENZOR.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported, and similar results may be expected with BENICAR, BENICAR HCT, AZOR, or TRIBENZOR.

BENICAR HCT is not recommended in patients with severe renal impairment. Avoid use of TRIBENZOR in patients with severely impaired renal function (creatinine clearance ≤30 mL/min). If progressive renal impairment becomes evident, consider withholding or discontinuing TRIBENZOR.

Sprue-like Enteropathy: Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, exclude other etiologies. Consider discontinuation of BENICAR, BENICAR HCT, AZOR, or TRIBENZOR in cases where no other etiology is identified.

Hepatic Impairment: Initial therapy with AZOR or TRIBENZOR is not recommended in hepatically impaired patients. In patients with severe hepatic impairment, exercise caution with AZOR and avoid use of TRIBENZOR. Thiazides (a component in BENICAR HCT and TRIBENZOR) should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Electrolyte and Metabolic Imbalances: Due to the hydrochlorothiazide (HCTZ) component in BENICAR HCT and TRIBENZOR, observe patients for clinical signs of metabolic, fluid, or electrolyte imbalance.

Hypersensitivity Reaction: Hypersensitivity reactions to HCTZ (a component in BENICAR HCT and TRIBENZOR) may occur in patients with or without a history of allergy or bronchial asthma.

Systemic Lupus Erythematosus: Thiazides (a component in BENICAR HCT and TRIBENZOR) have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Acute Myopia and Secondary Angle-Closure Glaucoma: Thiazides can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Discontinue HCTZ (a component in BENICAR HCT and TRIBENZOR) as rapidly as possible in these patients.

Vasodilation: Although vasodilation attributable to amlodipine (a component in AZOR and TRIBENZOR) is gradual in onset, acute hypotension has rarely been reported after oral administration. Patients with severe aortic stenosis may be at particular risk.

Increased Angina and/or Myocardial Infarction: Patients taking AZOR or TRIBENZOR, particularly those with severe obstructive coronary artery disease, may develop increased frequency, duration, or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dose increase.

Laboratory Tests: There was a greater decrease in hemoglobin and hematocrit with AZOR compared to either component alone. Other lab abnormalities may include increased blood creatinine levels and hyperkalemia (olmesartan medoxomil), hepatic enzyme elevations (amlodipine), and increased cholesterol and triglyceride levels (HCTZ).

DRUG INTERACTIONS

Non-Steroidal Anti-Inflammatory Agents: Concurrent administration of non-steroidal anti-inflammatory drugs (NSAIDs) may lead to increased risk of renal impairment (including possible acute renal failure) and loss of antihypertensive effect of BENICAR, BENICAR HCT, AZOR, and TRIBENZOR.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on BENICAR, BENICAR HCT, AZOR, or TRIBENZOR and other agents that affect the RAS.

Avoid use of aliskiren with BENICAR, BENICAR HCT, AZOR, or TRIBENZOR in patients with renal impairment (GFR <60 mL/min).

Concurrent Use with Colesevelam Hydrochloride: Concurrent administration of colesevelam hydrochloride with BENICAR, BENICAR HCT, AZOR, or TRIBENZOR reduces the systemic exposure and peak plasma concentration of olmesartan. Consider administering olmesartan at least 4 hours before the colesevelam hydrochloride dose.

Effect of Amlodipine on Simvastatin: Due to increased exposure to simvastatin, when co-administered with amlodipine (a component in AZOR and TRIBENZOR), do not exceed doses of greater than 20 mg daily of simvastatin.

Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of olmesartan or thiazide diuretics. Monitor lithium levels in patients receiving BENICAR, BENICAR HCT, AZOR, or TRIBENZOR and lithium.

ADVERSE REACTIONS

BENICAR: The only adverse reaction that occurred in >1% of patients treated with BENICAR and more frequently than placebo was dizziness (3% vs 1%).

BENICAR HCT: Adverse reactions reported in >2% of patients taking BENICAR HCT and more frequently than placebo included nausea (3% vs 0%), hyperuricemia (4% vs 2%), dizziness (9% vs 2%), and upper respiratory tract infection (7% vs 0%).

AZOR: The most common adverse reaction (incidence ≥3%) in patients treated with AZOR was edema.

TRIBENZOR: The most frequently reported adverse reaction was dizziness (5.8% to 8.9%). The other most frequent adverse reactions occurring in ≥2% of patients treated with TRIBENZOR were peripheral edema (7.7%), headache (6.4%), fatigue (4.2%), nasopharyngitis (3.5%), muscle spasms (3.1%), nausea (3.0%), upper respiratory tract infection (2.8%), diarrhea (2.6%), urinary tract infection (2.4%), and joint swelling (2.1%).

USE IN SPECIFIC PATIENT POPULATIONS

Nursing Mothers: Avoid use while nursing; discontinue either nursing or the drug.

Please see Full Prescribing Information for BENICAR, BENICAR HCT, AZOR, and TRIBENZOR.

References:
[1] American Heart Association. Heart Disease and Stroke Statistics: 2015. *Circulation*. 2015. 131:e29-e322.
[2] Weber MA, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens*. 2014 Jan;16(1):14-26.

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